

68. A method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence of claim 52, the method comprising:

- a) exposing a sample comprising the target polynucleotide to a compound, and
- b) detecting altered expression of the target polynucleotide. -

REMARKS

The Invention

Applicants' invention comprises, *inter alia*, human DnaJ-like proteins (hereinafter referred to as HSPJ1 and HSPJ2, and collectively, as HSPJ), the polynucleotides encoding HSPJ, and variants thereof for the diagnosis of acquired and inherited disease, expression profiling, and drug development. HSPJ are human homologues of the DnaJ component of the bacterial Hsp70 heat shock protein complex (DnaK/DnaJ/GrpE), a well characterized bacterial chaperone used as a model for eukaryotic cellular chaperones. Applicants' invention is described in detail throughout the specification of the above identified application.

Amendments to Claims

Claims 43-61 and 65 are pending in the above identified application (note that claims 62-64 are canceled herein). Claims 45-49, 52-56, and 65 (Group II) were provisionally elected by verbal restriction. Claims 45 and 49 were objected to as being dependent upon non-elected claim 43. Claims 45 and 49 have been amended herein to obviate this dependency. Applicants appreciate the Examiner's efforts to expedite prosecution of the application by examining claims 45 and 49 prior to amendment.

Newly added claims 66-68 are drawn to methods of use of the polynucleotides of claim 52. Support for these claims is found throughout the specification, in particular on pages 4-6, 16-21, and 52-54. Applicants request examination of these newly added claims along with the other claims drawn to methods of use of the polynucleotides of claim 52 (i.e., claims 54-56). No new matter is added by these amendments.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 45, 47-49, and 52-56 stand rejected under 35 U.S.C. § 112, first paragraph. The rejection alleges in particular that:

"Claims 45, with dependent claims 47-48, claim 49, and claim 52, with dependent claims 53-56 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of DNA molecules with either SEQ ID NOS: 2 or 4; or DNA having the limitations of encoding a protein having the SEQ ID NOS: 1 or 3; or any DNA which is 90% identical to SEQ ID Nos:2 or 4; or encodes a protein that is 90% identical to SEQ ID Nos:1 or 3." [page 5]

Claims 45, 49 and 52 are further rejected under 35 U.S.C. § 112, first paragraph, as detailed below:

"Claims 45, 49, and 52 are drawn to a DNA encoding both a polypeptide having an enzymatic activity and an inactive variant thereof. The specification does not teach how to use said inactive variant. Therefore, the breadth of these claims is much larger than the scope enabled by the specification." [page 6, Office Action]

The Examiner has already conceded that the specification is enabling for DNAs encoding SEQ ID NO:1 and SEQ ID NO: 3 (page 6, of Office Action); therefore, the remaining issues pertain to:

- a) Whether the specification adequately discloses and teaches to one skilled in the art that Applicant had possession of HSPJ polynucleotide variants with at least 90% identity to SEQ ID NO:2 and SEQ ID NO:4 or polynucleotide variants encoding polypeptides with at least 90% identity to SEQ ID NO:1 and SEQ ID NO:3.
- b) Whether the specification teaches to one skilled in the art how to use naturally occurring polynucleotide variants of SEQ ID NO:2 or SEQ ID NO:4 that encode inactive variants of the polypeptides of SEQ ID NO:1 and SEQ ID NO:3.

Applicants submit that these categories of variants (which are not mutually exclusive) would be obvious to one skilled in the art based on the disclosure of the polypeptides of SEQ ID

NO:1 and SEQ ID NO:3 and the polynucleotides of SEQ ID NO:2 and SEQ ID NO: 4 encoding them, respectively, as would be the use of these polynucleotide sequences, e.g., in toxicology testing, expression profiling, drug development, and the diagnosis of disease, so as to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph.

a) Written Description

The rejection of claims 45, 47-49, and 52-56 is improper, as the instant application satisfies the written description requirement for both active and inactive naturally occurring variants of HSPJ which have real world utilities that are well-known to one of ordinary skill in the art.

The invention at issue is a **polynucleotide** sequence corresponding to a **gene** that is expressed predominantly in immortalized or cancerous humans tissues. As such, the claimed invention, including naturally occurring variants of the specified sequence, has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which necessarily require detailed knowledge of how the polypeptide coded for by the polynucleotide works. Furthermore, as a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

As to whether Applicants have possession of the claimed naturally occurring variants having 90% sequence identity to the sequences of SEQ ID NO:2 and SEQ ID NO:4, it is respectfully submitted that, based on the specification and its teachings, it would be a very simple matter for one of ordinary skill in the art to find naturally occurring sequences having 90% sequence identity to SEQ ID NO:2 and SEQ ID NO:4. See for example, the specification on pages 48-49, and 52-53, which teach how to find and identify HSPJ sequences based on using probes complementary to SEQ ID NO:2 or SEQ ID NO:4. Similarly, based on these teachings, it would be routine and without undue experimentation to determine whether a naturally occurring sequence thus obtained is a sequence that is 90% identical to the sequence of SEQ ID NO:2 or SEQ ID NO:4. No doubt, such variants may be many in number, but it would not be an impractical or undue task to identify such variants given current computing technology, thus one of ordinary skill would readily know which variants were encompassed by the present claims,

and thus the written description requirements are met. Applicants respectfully request that the rejection be withdrawn.

b) Enablement

In recent years, scientists have developed important techniques for toxicology testing, drug development, and disease diagnosis. Many of these techniques rely on expression profiling, in which the expression of numerous genes is compared in two or more samples. Genes or gene fragments known to be expressed, such as the invention at issue, are tools essential to any technology that uses expression profiling. Knowledge of the function of the polypeptide that a polynucleotide encodes is not necessary for the use of the polynucleotide in expression profiling. The fact that the expression profile of a naturally occurring polynucleotide is altered in a sample treated with a test compound is highly relevant in toxicology testing even in the absence of a known function for the encoded polypeptide.

Likewise, proteome expression profiling techniques have been developed in which the expression of numerous polypeptides is compared in two or more samples. Polypeptide or polypeptide fragments known to be expressed are tools essential to any technology that uses proteome expression profiling. See, *e.g.*, Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467 (2000).

The technologies made possible by expression profiling and the DNA and polypeptide tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. One of these techniques is toxicology testing, used in both drug development and safety assessment. Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29(7):655, 656 (1999):

Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Genesis 24:153 (1999); Sandra Steiner and N. Leigh Anderson, *supra*.

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

... for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

This Human ToxChip also included 23 heat shock proteins, underscoring the real world utility of the polynucleotides of the instant application (see Table 1 of Nuwaysir et al.).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107(8):681 (1999). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening. This is true for both polynucleotides and polypeptides encoded by them. Knowledge of the function of the polypeptide that a polynucleotide encodes is not necessary for the use of the polynucleotide in expression profiling or toxicological screening. Moreover, knowledge of the function of naturally occurring protein variants having at least 90% homology to a known polypeptide is not necessary for the use of the polynucleotides encoding them for expression profiling or toxicological screening.

There are numerous uses for the information made possible by expression profiling. Expression profiling is used to identify drug targets and characterize disease. See Rockett et al., *supra*. It also is used in tissue profiling, developmental biology, disease staging, etc. The use of a polynucleotide that encodes an inactive variant of a polypeptide (e.g., an inactive form of HSPJ) may be of particular value for these purposes. Using such variant polynucleotides (e.g., as components of a microarray) to determine whether a patient is expressing a defective or inactive gene, in addition to or in place of the active form, and determining the expression levels of these genes, is a powerful tool in diagnosing disease. Similarly, the use of other polynucleotide sequence variants (e.g., with at least 90% homology to HSPJ, as disclosed in the specification of the instant application), whether these sequences encode active or inactive polypeptides, is similarly useful in expression profiling and in diagnosing disease based on the HSPJ variants expressed by an individual. The expression of such variants may be associated with (i) alternative splicing, (ii) the use of internal promoter elements, (iii) RNA editing, (iv) chromosomal deletion or translocation, (v) spontaneous or environmentally induced mutations, or other events that alter gene expression. The use of polynucleotide variants is particularly useful in identifying genetic polymorphisms (including but not limited to single nucleotide polymorphisms (SNP, SNiPs)) that are useful genotypic markers for genetic abnormalities. The use of HSPJ polynucleotide variants, based on the disclosure of the polynucleotides of SEQ ID NO:2 and SEQ ID NO:4, would be readily apparent to a practitioner skilled in the art.

Expression profiling technology is also used to identify drug targets and analyze disease at the molecular level, thus accelerating the drug development process. For example, expression profiling is useful for the elucidation of biochemical pathways, each pathway comprising a multitude of component polypeptides and thus providing a pool of potential drug targets. In this manner, expression profiling leads to the optimization of drug target identification and a comprehensive understanding of disease etiology and progression. Again, the use of variant polynucleotide sequences, based on the disclosure of the polynucleotides of SEQ ID NO:2 and SEQ ID NO:4, would be readily apparent to a practitioner skilled in the art in order to search for variant alleles, acquired and inherited genetic polymorphisms, and mutations that alter the function of an HSPJ polypeptide.

Applicants recognize that not all broad classes of inventions are, by themselves, sufficient to inform a person of ordinary skill in the art of the practical utility for a member of the class. Some classes may indeed convey too little information to a person of ordinary skill in the art. These may include classes of inventions that include both useful and nonuseful members. *See In re Ziegler*, 992 F.2d 1197, 1201, 26 USPQ2d 1600 (Fed. Cir. 1993). In some of these cases, further experimentation would be required to determine whether or not a member of the class actually has a practical use. *Brenner*, 383 U.S. at 534-35.

The broad class of steroids identified in *Kirk* is just such a class (*In re Kirk*, 376 F.2d 936, 945, 153 USPQ 48 (C.C.P.A. 1967)). It includes natural steroids (concededly useful) and man-made steroids, some of which are useful and some of which are not. Indeed, only a small fraction of the members of this broad class of invention may be useful. Without additional information or further experimentation, a person of ordinary skill in the art would not know whether a member of the class falls into the useful category or not. This could also be the case for the broad class of "plastic-like" polypropylenes in *Ziegler*, which includes many -- perhaps predominately -- useless members.

The PTO routinely issues patents whose utility is based solely on the claimed inventions' membership in a class of useful things. The PTO presumably would issue a patent on a novel and nonobvious fishing rod notwithstanding the lack of any disclosure of the particular fish it might be used to catch. The standard being promulgated in the Guidelines and in particular as exemplified in the Training Materials, and being applied in the present rejection, would appear to warrant a rejection, however, on the grounds that the use of the fishing rod is applicable to the general class of devices used to catch fish.

The PTO must apply the same standard to the biotechnological arts that it applies to fields such as plastics and fishing equipment. *In re Gazave*, 379 F.2d 973, 977-78, 154 USPQ 92 (CCPA 1967) quoting *In re Chilowsky*, 299 F.2d 457, 461, 108 USPQ 321 (CCPA 1956) ("[T]he same principles should apply in determining operativeness and sufficiency of disclosure in applications relating to nuclear fission art as in other cases."); see also *In re Alappat*, 33 F.3d 1526, 1566, 31 USPQ2d 1545 (Fed. Cir. 1994) (Archer, C.J., concurring in part and dissenting in part) ("Discoveries and inventions in the field of digital electronics are analyzed according to the aforementioned principles [concerning patentable subject matter] as any other subject matter.").

Indeed, there are numerous classes of inventions in the biotechnological arts that satisfy the utility requirement.

Take, for example, the class of interleukins expressed in human cells of the immune system. Unlike the classes of steroids or plastic-like polypropylenes in *Kirk* and *Ziegler*, all of the members of this class have practical uses well beyond “throwaway” uses. All of them cause some physiological response (in cells of the immune system). All of the genes encoding them can be used for toxicology testing to generate information useful in activities such as drug development, even in cases where little is known as to how a particular interleukin works. No additional experimentation would be required, therefore, to determine whether an interleukin has a practical use. It is well-known to persons of ordinary skill in the art that there is no such thing as a useless interleukin.

Because all of the interleukins, as a class, convey practical benefit (much like the class of DNA ligases identified in the Training Materials), there is no need to provide additional information about them. A person of ordinary skill in the art need not guess whether any given interleukin conveys a practical benefit or how that particular interleukin works.

Another example of a class that by itself conveys practical benefits is the G protein-coupled receptors (“GPCRs”). GPCRs are well-known as intracellular signaling mediators with diverse functions critical to complex organisms. They perform these functions by binding to and interacting with specific ligands. They are targets of many current drug treatments, including anti-depressants, anti-histamines, blood pressure regulators, and opiates.

Newly-identified GPCRs are used intensively in the real-world, even in cases where neither the specific ligand that binds to the GPCR or the precise biological function of the GPCR is known. Newly identified GPCRs are used, for example, as toxicity controls for drug candidates known to bind other GPCRs. Because a person of ordinary skill in the art would know how to use any GPCR to achieve a practical benefit, even without any detailed or particular knowledge as to how it works, GPCRs as a class meet the utility requirement.

In fact, **all** isolated and purified naturally-occurring polynucleotide and polypeptide sequences which are expressable (i.e., which are not pseudogenes that are never expressed during any natural biological process) can be and **are** used in a real-world context as tools for toxicological testing, e.g., for drug discovery purposes. This utility applies to all sequences actually

expressed, yet in each case, the utility of the sequence is quite specific, e.g., insofar as it is used to detect its own specific complementary sequence in a sample containing many different sequences.

Cellular chaperones, like interleukins, GPCRs and fishing rods is a class that by itself conveys practical benefits. Unlike steroids and “plastic-like” polypropylenes, all polynucleotides encoding cellular chaperones identified from a cDNA library prepared from human tissues are, by definition, expressed by humans, and all such polynucleotides can be used as tools for toxicology testing, expression profiling, and screening for inherited or acquired genetic diseases. The claimed invention could be used, for example to determine whether a drug candidate affects the expression of cellular chaperones in humans, how it does so, and to what extent. Just as there are no useless polynucleotide sequences encoding interleukins and GPCRs, there are no useless polynucleotides encoding cellular chaperones. Even those polynucleotides encoding naturally occurring but inactive variant cellular chaperones are useful for toxicology testing, expression profiling, and disease diagnosis (and perhaps even more so). As these are practical, real-world uses, the application need not describe particular functionality or medical applications that would only supplement the utilities known to exist already.

The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Not Know How to Use of Some Elements of the Claimed Invention

In addition to alleging a “specific” use for the claimed subject matter, a patent applicant must present proof that the claimed subject matter is in fact useful. *Brana*, 51 F.3d at 1565-66. The applicant need only prove a “substantial likelihood” of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

The amount of evidence required to prove utility depends on the facts of each particular case. *In re Jolles*, 628 F.2d 1322, 1326, 206 USPQ 885 (CCPA 1980). “The character and amount of evidence may vary, depending on whether the alleged utility appears to accord with or to contravene established scientific principles and beliefs.” *Id.* Unless there is proof of “total incapacity,” or there is a “complete absence of data” to support the applicant’s assertion of utility, the utility requirement is met. *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 USPQ2d 1401 (Fed. Cir. 1992); *Envirotech*, 730 F.2d at 762.

A patent applicant's assertion of utility in the disclosure is presumed to be true and correct. *In re Cortright*, 165 F.3d at 1356; *Brana*, 51 F.3d at 1566. If such an assertion is made, the Patent Office bears the burden in the first instance to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. *See Langer*, 503 F.2d at 1391-92. If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The Revised Guidelines are in agreement with this procedure. *See Revised Interim Guidelines at ¶¶ 3-4.*

The issue of proof often arises in the chemical and biotechnological arts when the patentee asserts a utility for a claimed chemical compound based on its homology or similarity to another compound having a known, established utility. In such cases, the applicant can demonstrate "substantial likelihood" of utility by demonstrating a "reasonable correlation" between the utility -- not the function -- of the known compound and the compound being claimed. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 USPQ2d 1895 (Fed. Cir. 1996). Accordingly, under *Brana*, the Patent Office must accept the asserted utility unless it can show that a person of ordinary skill in the art would reasonably doubt that a "reasonable correlation" exists. If the Patent Office makes such a showing, however, the applicant may submit evidence in support of the correlation.

In the present case, the Examiner asserts that one of ordinary skill in the art would not know how to use a variant HSPJ polynucleotide sequences encoding inactive polypeptides or variant polynucleotides that are at least 90% homologous to the polynucleotides of SEQ ID NO:2 or SEQ ID NO:4 (or that encode polypeptides at least 90% homologous to the polypeptides of SEQ ID NO:1 or SEQ ID NO:3). Applicants have argued that there is a real world utility for these variant polynucleotides, including but not limited to screening for congenital or inherited genetic diseases characterized by altered polynucleotide expression patterns and/or the expression of polynucleotide sequence variants (including but not limited to single nucleotide polymorphisms that may lead to the expression of inactive proteins), toxicology screening, expression profiling, and use for chromosomal markers, probes, and forensic tools. These utilities are independent of whether the encoded polypeptides are active or inactive. In fact, the

use of variant polynucleotide sequences encoding inactive variant polypeptides, or polypeptides with altered substrate specificity, catalytic properties, stability, or antigenic properties may make such polynucleotide especially valuable for microarrays to screen for inherited or acquired genetic diseases.

By ignoring the “reasonable correlation” requirement in the case law and failing to illustrate the procedure established by *Brana*, the Examiner has failed to set forth a proper *prima facie* case, and the rejection does not shift the burden of proof to Appellants for rebuttal. In fact, the rejection must be withdrawn, as the Examiner has failed to meet PTO’s burden in the first place of establishing a proper rejection. There is no proper rejection for Appellants to rebut.

Because the Patent Examiner failed to address or consider the “well-established” utilities for portions of the claimed invention drawn to active and inactive naturally occurring variants of HSPJ in toxicology testing, drug development, and the diagnosis of disease, and the obviousness to one skilled in the art of making and testing such variant polynucleotides, the Examiner’s rejections should be overturned.

Nonstatutory Double Patenting Rejection

Claims 45-49, 52, and 53 stand rejected under the judicially-created doctrine of double patenting over claims 1-9 of the parent application (U.S. Patent No. 5,922,567). Applicants submit that claim 45 (and dependent claims 46-48, 50, and 65), 49, and 52 (and dependent claims 53-56, along with newly added claims 66-67), drawn to polynucleotides, are clearly of a different scope than those allowed in the parent application. Furthermore, claims 54-56 are drawn to methods of use that were examined but not allowed in the parent application. Applicants submit that these method claims should have been allowed, along with claims directed to the polynucleotide, per the Commissioner’s Notice in the Official Gazette of March 26, 1996, entitled “Guidance on Treatment of Product and Process Claims in light of *In re Ochiai*, *In re Brouwer* and 35 U.S.C. § 103(b)” which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products. Allowance of claims 54-56, along with newly added claims 66-67, all drawn to methods of use of the polynucleotides of the instant application will remedy this oversight.

In the event the Examiner maintains the objection based on nonstatutory double patenting, despite Applicants' assertion that the claims drawn to polynucleotides in the instant application are of a different scope than the allowed claims of the issued patent, Applicants will overcome the objection by filing a terminal disclaimer in compliance with 37 CFR § 1.321(c).

CONCLUSION

Appellants respectfully submit that rejections of portions of the claims drawn to polynucleotides encoding inactive HSPJ variants and polynucleotides with at least 90% homology to SEQ ID NO:2 or SEQ ID NO:4 (or encoding polypeptides with at least 90% homology to SEQ ID NO:1 or SEQ ID NO:3) for lack of utility based, *inter alia*, on an allegation of "lack of specificity" as set forth in the Office Action and as justified in the Revised Interim Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to draw inaccurate parallels between the facts of these prior cases and pending applications to support unfounded rejections of claims to polypeptide and polynucleotide sequences where biological activity information has not been proven by laboratory experimentation. It has done so by ignoring perfectly acceptable utilities fully disclosed in the specifications as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

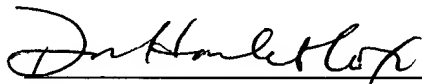
Applicants note that the portions of claims 45, 47-49, and 52-56, drawn specifically to the polynucleotides of SEQ ID NO:2 and SEQ ID NO:4, appear to be in condition for allowance. If the Examiner refuses to allow the portions of these claims directed to variants of these polynucleotides, despite Applicants arguments, then Applicants provisionally elect to prosecute the portions of the claims that are allowed. Lastly, Applicants note that there were no objections to claim 65 in the Office Action.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650)855-0555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108**. This form is enclosed in duplicate.

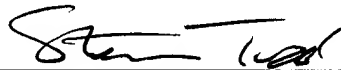
Respectfully submitted,
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